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(54) Title: AN IMPROVED PROCESS FOR PRODUCING HEPTASTIGMINE AND A NEW INTERMEDIATE COMPOUND USEFUL IN THIS PROCESS

(57) Abstract

An improved process for producing heptastigmine and acid addition salts thereof with organic acids, wherein the improvement consists in that the preparation of heptastigmine from physostigmine is carried out by reacting heptastigmine with a suitable silylating agent and the silyl group of the thus obtained silyl compound is then replaced with a hydrogen atom. Advantageously, the subsequent addition of heptyl isocyanate to eseroline is carried out in the presence of a base and a polar aprotic diluent.

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"An improved process for producing heptastigmine and a new intermediate compound useful in this process"

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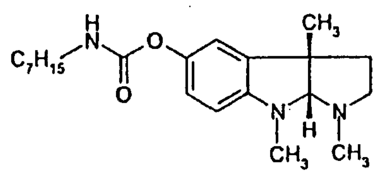
The present invention relates to an improved process for producing heptastigmine and a new intermediate compound useful in said process.

In the present description and in the claims attached thereto the term heptastigmine is used to mean 1,3a,8-trimethyl-1,2,3,3a,8a-hexahydropyrrole[2,3-b]indol-5(3aS,8aR)-heptylcarbamate of formula:



(I)

Heptasigmine and the acid addition salts thereof with organic acids inhibit acetylcholine esterase and are particularly useful for treating Alzheimer disease.

EP-A-O 154 864 discloses the preparation of heptastigmine by hydrolyzing physostigmine (also known as eserine) with a salt of an alkaline alkoxylate compound under vacuum. The thus obtained eseroline alkaline salts are then reacted, still under vacuum, with heptyl isocyanate in the presence of a polar hydrocarbon solvent medium, preferably benzene. The total yield ranges from 40 to 70%.

EP-A-O 298 202 mainly refers to heptastigmine acid addition salts with organic acids. However, it also aims to overcome some drawbacks of the process disclosed by EP-A-O 154 864 (need of performing all the synthesis under vacuum and low yields). To this purpose, EP-A-O 298 202 discloses to hydrolyze physostigmine into an organic solvent, particularly a lower aliphatic alcohol or glycol, with alkalies under nitrogen, followed by treatment with a strong inorganic acid. This

hydrolysis has the drawback of being exothermic and difficult to control on a large scale. The thus obtained crude eseroline is then purified by crystallization from a mixture of aromatic and aliphatic hydrocarbons, preferably benzene/ petrolium ether 1 : 1. The subsequent eseroline reaction with heptyl isocyanate is carried on by dissolving separately the first two crude compounds into an organic solvent, preferably ethyl ether. To the eseroline solution there is added at first a catalytic amount of an alkaline compound, preferably sodium metal, and then, under nitrogen, an isocyanate solution. The total yield ranges from 70 to 80%.

In order to overcome the drawbacks implied by the use of ethyl ether and sodium metal, EP-A-O 499 179 suggests to perform the reaction of eseroline with heptyl isocyanate, optionally prepared *in situ* from 1-bromoheptane and potassium cyanate, into a polar aprotic solvent, preferably acetonitrile or ethyl acetate, and in the presence of a catalytic amount of a quaternary ammonium salt as well as of a metal cyanate or alcoholate. This reaction is also carried out under nitrogen for 8 hours when heptyl isocyanate is used or 19 hours, under reflux, when the latter is prepared *in situ*.

The process described by this patent has the main drawback of using eseroline produced according to known technique: that means, produced under vacuum according to EP-A-O 154 864 or by the exothermic reaction according to EP-A-O 298 202. Further, as already mentioned, the reaction between eseroline and heptyl isocyanate described by EP-A-O 499 179 implies quite long times.

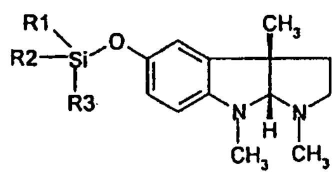
In order to produce heptastigmine and the salts thereof on a large scale, it is still felt the need of a process wherein eseroline is produced without working under vacuum or without having to control an exothermic reaction. Further, it is also very felt the need of reducing the time of the reaction of eseroline with heptyl isocyanate.

Now, it has been unexpectedly found that these drawbacks may be overcome by the present invention that provides an improved process for producing heptastigmine and acid addition salts thereof with organic acids comprising:

1) preparing eseroline from physostigmine,
2) adding heptyl isocyanate to eseroline to afford heptastigmine and
3) when desired, forming an acid addition salts of heptastigmine with an organic acid,

wherein the improvement is that the step (1) is carried on

a) by reacting physostigmine with a suitable silylating agent to afford a compound of formula



(II)

wherein R_1, R_2 and R_3, the same or different, are a lower alkyl, a lower alkylene or an aryl, and

b) then by replacing into the thus obtained compound of formula (II) the group $SiR_1R_2R_3$ with a hydrogen atom.

Preferred examples of R_1, R_2 and R_3 are methyl, ethyl, propyl, butyl, vinyl and phenyl. Most preferably, R_1, R_2 and R_3 are methyl.

Examples of suitable silylating agents are disilazane such as, for example, 1,3-dimethyl-1,1,3,3-tetraphenyldisilazane, 1,3-diphenyl-1,1,3,3-tetramethyldisilazane, 1,3-divinyl-1,1,3,3-tetramethyldisilazane, and 1,1,1,3,3,3-hexamethyldisilazane (HDMS).

According to this invention, the preferred silylating agent is HDMS (1,1,1,3,3,3-hexadimethylsilazane). When the silylating agent is fluid, step 1a is preferably carried on by using, as a diluent, an excess of the silylating agent itself. However, the reaction can also be carried on in the presence of a suitable organic diluent or a suitable mixture of

organic diluents, which can be easily preselected by a person skilled in the art, case by case, depending on the silylating agent which is used and by simple experimental routine trials.

Reaction temperature and time of the step 1a will vary depending on the silylating agent and the possible diluents which are used, by parameters which are well known to the person skilled in the art.

Typically, in case of HDMS, the reaction can be carried on without adding any diluent at a temperature of from 100°C to 125°C, preferably at about 125°C, for 4 to 8 hours, preferably for about 6 hours.

Alternately, the reaction is carried out in the presence of a diluent selected from aromatic hydrocarbons such as, for example, toluene, xylene and tetrahydronaphthalene, at the reflux temperature of the reaction mixture. An example of a preferred diluent is toluene.

The molar ratio of physostigmine to HMDS is preferably of from 1 : 2 to 1 : 10. More preferably it is of 1 : 2.5.

Step 1a affords compound (II), which is a distillable oil, in an almost quantitative yield, together with N-methyl urea.

The compound of formula (II) is a new stable and protected derivative of eseroline. Therefore, it is a further object of the present invention to provide an intermediate compound of formula (II).

Step 1b is preferably carried on by methanolysis at room temperature for 1 hour. After removal of volatile products, the thus obtained crude eseroline can be transformed into heptastigmine (step 2) according to known techniques such as, for example, those described by EP-A-O 499 179.

However, it has now been unexpectedly found that when the addition reaction of heptyl isocyanate to eseroline (step 2) is carried out in the presence of a base and of a polar aprotic diluent the reaction time is substantially reduced compared to that required when the same reaction is carried on in a polar aprotic diluent but in the presence of a

system formed by (i) catalytic amounts of a quaternary ammonium salt and a metal cyanate or by (ii) catalytic amounts of a quaternary ammonium salt and a metal alcoholate.

Examples of suitable polar aprotic diluents are: acetonitrile, tetrahydrofuran and ethers of glycols such as 1,2-dimethoxyethane, 1,2-diethoxyethane, dioxane, diethylenglycol diethyl ether, diethylen glycol divinyl ether, diethylen glycol dimethyl ether (diglime) and triethylen glycol dimethyl ether.

Diglime is the preferred diluent.

Examples of suitable bases are: sodium hydride, sodium carbonate, potassium carbonate, sodium methoxide, triethylamine. The preferred base is potassium carbonate.

Typically, crude eseroline is taken up with diglime and added, in the presence of potassium carbonate and under nitrogen flushing, with heptyl isocyanate in a molar ratio of from 1 : 0.1 to 1 : 1 ; preferably 1 : 0.1.

The reaction may be carried on at a temperature of from 0° to 220°C, preferably of from 20° to 25°C.

After about 2 hours at room temperature, the reaction mixture is worked up to afford heptastigmine that can be transformed, when desired , into an acid addition salt thereof (step 3), such as tartrate, according to known techniques.

The easy quantitative substitution of the carbamic group (CH_3NH-CO) of physostigmine with $SiR_1R_2R_3$ (wherein R_1, R_2 and R_3 have the above mentioned meanings) group was completely unexpected and it is a main feature of the present invention because it allows overcoming all the drawbacks of the known techniques for preparing eseroline from physostigmine.

Another relevant feature of the present invention is the easy transformation of the silyl compound of esertoline (compound of formula (II)) into eseroline under mild conditions and with good yield.

A third relevant feature of the present invention is the short time required, even at room temperature, when crude eseroline is reacted with heptyl isocyanate in the presence of a base and of a polar aprotic diluent.

These and further features of the present invention will appear more evident from the following examples that are intended to illustrate the present invention without limiting it in any way.

Example 1

Preparation of trimethyl-1,3a, 8-hexahydro-1,2,3,3a,8,8a-pyrrole(2,3-b) indol-5-(3aS,8aR)trimethylsilylether.

(Compound of formula II, where $R_1 = R_2 = R_3 = CH_3$)

A suspension of physostigmine (2 g; 7.3 mmol) in HDMS (3.8 ml ; 18 mmol) was allowed to reflux under stirring for 6 hours. HDMS in excess was removed under vacuum. After addition of petrolium ether (5 ml), the suspension was kept under stirring at room temperature for 30 minutes. After filtering, the solution was evaporated to dryness to give 2 g (yield: 95% on the theoretical amount) of the desired compound, as a pale yellow oil, b.p. 124-126°C (0.4 mbar).

^{1}HNMR ($CDCl_3$) : δ= 0.22 (s, 9H) ; 1.40 (s, 3H) ; 1.92 (t, 2H) ; 2.67 (m, 2H) ; 2.88 (s, 3H) ; 4.00 (s, 1H) ; 6.28 (d, 1H) ; 6.52 (s, 1H) ; 6.74 (d, 1H).

IR spectrum (liquid film) : cm^{-1} 2958(s), 1493(s), 1252(s), 956(s).

Example 2

Preparation of trimethyl-1,3a,8-hexahydro-1,2,3,3a,8,8a-pyrrole(2,3-b)indol-5-(3aS, 8aR)trimethylsilylether.

(Compound of formula II, where $R_1 = R_2 = R_3 = CH_3$)

A solution of physostigmine (1g ; 3.65 mmol) and HDMS (1.9 ml ; 9 mmol) in 5 ml of toluene was allowed to reflux for 48 hours. The reaction mixture was then worked up as described in Example 1. It was thus obtained the desired compound. (Yield: 95% on the theoretical amount).

Example 3

Preparation of heptastigmine and tartrate salt thereof.

A solution of trimethyl-1,3a,8-hexahydro-1,2,3,3a,8,8a-pyrrole(2,3-b)indol-5-(3aS,8aR)trimethylsilylether (1.2 g ; 4.1 mmol) in methanol (12 ml) was kept under stirring at room temperature for 1 hour under a nitrogen stream, and then evaporated to give 0.9 g of eseroline. To the eseroline solution in diglime (18 ml) it was added potassium carbonate (0.09 g) and to the thus obtained mixture a heptyl isocyanate solution (0.79 ml, 4.9 mmol) in diglime (4ml) was added dropwise, in 15 minutes while maintaining under a reduced nitrogen stream. The reaction mixture was kept under stirring at room temperature for 2 hours, filtered and diluted with water (75 ml) and HCl 1 : 4 (0.1 ml) to remove diglime via azeotropic distillation under vacuum. The residue was taken up with water (50 ml) and extracted by dichloromethane (2 x 50 ml); the organic phase was washed with water (3 x 50 ml) and dried over sodium sulphate. After removal of the solvent under vacuum, the residue (1.3 g) was extracted by hot hexane (3 x 15 ml) for removing an impurity (N,N-diheptyl urea).

After evaporation of the solvent under vacuum, there were obtained 950 mg of heptastigmine (yield: 64% on the theoretical amount) as an oil that was transformed in the corresponding tartrate according to the process described by EP-A-O 298 202 (yield: 90% on theoretical amount computed on heptastigmine; m.p 121-123°C).

Example 4

Preparation of heptastigmine tartrate.

80 mg of heptastigmine tartrate were obtained by working in the same way as described in Example 3, starting from 0.5 g of trimethyl-1,3a,8-hexahydro-1,2,3,3a,8,8a-pyrrole(2,3-b)indol-5-(3aS, 8aR) trimethylsilylether and using sodium hydride (molar ratio 1 : 1 to eseroline formed during the reaction) instead of potassium carbonate.

Example 5

Preparation of heptastigmine tartrate

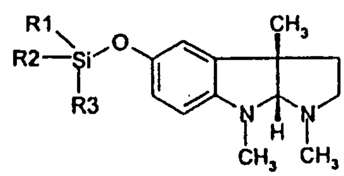
A solution of trimethyl-1,3a,8-hexahydro-1,2,3,3a,8,8a-pyrrole(2,3-b)indol-5-(3aS, 8aR)trimethylsilylether (II) (0.6 g; 2.05 mmol) in methanol (6 ml) was kept under stirring at room temperature and under a nitrogen stream for 1 hour. After evaporating of methanol under vacuum, the thus obtained crude eseroline (0.45 g) was dissolved in 5 ml of acetonitrile. After addition of triethylamine (0.29 ml ; 2.05 mmol) The solution, was kept under stirring at room temperature for 30 minutes. Then, to this solution it was added dropwise in 10 minutes a solution of heptyl isocyanate (0.4 ml; 2.5 mmol) in 2 ml of acetonitrile and the reaction mixture was kept under stirring for 2 hours.

After evaporation under vacuum, the residue was worked up as described in the Example 3. Yield: 0.2 g of heptastigmine tartrate.

CLAIMS

1. An improved process for producing heptastigmine and acid addition salts thereof with organic acids comprising:
   1) preparing eseroline from physostigmine,
   2) adding heptyl isocyanate to eseroline to afford heptasigmine, and
   3) when desired, forming an acid addition salt of heptastigmine with an organic acid,

   wherein the improvement is that the step 1 is carried on
   a) by reacting physostigmine with a suitable silylating agent to afford a compound of formula



(II)

   wherein R_1, R_2 and R_3, the same or different, are a lower alkyl, a lower alkylene or aryl ; and
   b) then replacing into the thus obtained compound of formula (II), the group $SiR_1R_2R_3$ with a hydrogen atom.
2. A process according to claim 1, characterized in that R_1, R_2 and R_3 are methyl, ethyl, propyl, butyl, vinyl and phenyl.
3. A process according to claim 1 or 2, characterized in that the silylating agent is a disilazane.
4. A process according to any one of claims 1 to 3, characterized in that the silylating agent is selected from the group comprising 1,3-dimethyl-1,1,3,3-tetraphenyldisilazane, 1,3-diphenyl-1,1,3,3-tetramethyldisilazane, 1,3-divinyl-1,1,3,3-tetramethyldisilazane and 1,1,1,3,3,3-hexamethyldisilazane (HDMS).
5. A process according to any one of claims 1-3, characterized in that the silylating agent is HDMS.

6. A process according to any one of claims 1 to 4, characterized in that phase 1a is carried on in the presence of at least a diluent.
7. A process according to claim 6, characterized in that the diluent is an aromatic hydrocarbon.
8. A process according to claim 7, characterized in that the aromatic hydrocarbon is toluene, xylene or tetrahydro naphthalene.
9. A process according to any one of the previous claims from 1 to 8, characterized in that phase 1a is carried on at the reflux temperature of the reaction mixture.
10. A process according to any one of the claims 1 to 4, characterized in that phase 1a is carried on without diluents at a temperature of from 100° to 125°C.
11. A process according to claim 5, characterized in that the molar ratio of physostigmine to HMDS is of from 1 : 2 to 1 : 10.
12. A process according to claim 11, characterized in that the physostigmine/ HDMS molar ratio is 1 : 2.5.
13. A process according to any one of the previous claims from 1 to 12, characterized in that phase 1b is carried on by methanolysis.
14. A process according to claim 13, characterized in that phase 1b is carried on at room temperature for 1 hour.
15. A process according to any one of the previous claims from 1 to 14, characterized in that phase 2 is carried on in the presence of a base and of a polar diluent.
16. A process according to claim 15, characterized in that the polar aprotic diluent is selected from the group comprising acetonitrile, tetrahydrofuran and ethers of glycols.
17. A process according to claim 16, characterized in that the ether of a glycol is selected from the group comprising 1,2-dimethoxyethane, 1,2-diethoxyethane, dioxane, diethylen glycol diethyl ether, diethylen glycol divinyl ether, diethylen glycol diethyl ether,

diethylen glycol divinyl ether, diethylen glycol dimethyl ether (diglime) and triethylen glycol dimethyl ether.

18. A process according to claim 15, characterized in that the polar aprotic diluent is diglime.

19. A process according to any one of the claims from 15 to 18, characterized in that the molar ratio eseroline/ heptyl isocyanate is of from 1 : 1.05 to 1 : 2.

20. A process according to claim 19, characterized in that the molar ratio eseroline/heptyl isocyanate is 1 : 1.2.

21. A process according to any one of the previous claims from 15 to 20, characterized in that the addition reaction is carried on at a temperature of from 0° to 160°C.

22. A process according to claim 21, characterized in that the addition reaction is carried on at a temperature of from 20° to 25°C.

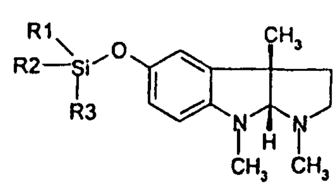
23. A process according to any one of the previous claims from 15 to 22, characterized in that the base is selected from the group comprising sodium hydride, sodium carbonate, potassium carbonate, sodium methoxyde and triethyl amine.

24. A process according to any one of the previous claims from 15 to 22, characterized in that the base is potassium carbonate.

25. A process according to any one of the previous claims from 15 to 24, characterized in that the molar ratio eseroline/ base is of from 1 : 0.1 to 1 : 1.

26. A process according to claim 25, characterized in that the molar ratio eseroline/ base is 1 : 0.1.

27. A compound of formula



(II)

wherein R_1, R_2 and R_3, the same or different, are a lower alkyl, a lower alkylene or an aryl.

28. A compound according to claim 27, characterized in that R_1, R_2 and R_3 are methyl, ethyl, propyl, butyl, vinyl or phenyl.
29. A compound according to claim 27, characterized in that R_1, R_2 and R_3 are the same and are methyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/04296

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 499 179 A (LABORATORIO CHIMICO INTERNAZIONALE S.P.A.) 19 August 1992 cited in the application * whole document * ---	1-29
A	EP 0 154 864 A (CONSIGLIO NAZIONALE DELLE RICHERCHE) cited in the application see claims; example 6 ---	1-29
A	EP 0 298 202 A (MEDIOLANUM FARMACEUTICI) cited in the application see claims; examples -----	1-29

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 February 1997	24.02.97

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/04296

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-499179	19-08-92	IT-B- 1244746	08-08-94
		AT-T- 125810	15-08-95
		AU-A- 1196992	15-09-92
		DE-D- 69203856	07-09-95
		DE-T- 69203856	21-12-95
		WO-A- 9214735	03-09-92
		EP-A- 0571434	01-12-93
		ES-T- 2077398	16-11-95
EP-A-154864	18-09-85	EP-A- 0354594	14-02-90
		JP-C- 1690155	27-08-92
		JP-B- 3054952	21-08-91
		JP-A- 60208982	21-10-85
		US-A- 5306825	26-04-94
		US-A- 4831155	16-05-89
EP-A-298202	11-01-89	AT-T- 110725	15-09-94
		CA-A- 1331616	23-08-94
		DE-D- 3851279	06-10-94
		DE-T- 3851279	09-02-95
		ES-T- 2060616	01-12-94
		IE-B- 64617	23-08-95
		JP-A- 1025777	27-01-89
		JP-B- 8026023	13-03-96
		KR-B- 9607865	13-06-96
		US-A- 4978673	18-12-90